REMARKS

Prior to entry of the claim amendments presented above, claims 1-32 were pending in the application. Claims 1-32 were rejected. In the present amendment, claims 33-47 have been added. Upon entry of the present amendment, claims 1-47 are pending.

Rejections Under 35 USC §112, First Paragraph

Claims 1-32 stand rejected under 35 USC § 112, first paragraph, for lack of enablement. As explained below, applicants urge that this rejection is improper because the disclosure and examples of the specification enable one of skill in the art to practice the invention within the scope of the claims.

Alleged Non-Enablement Due to Low Expression of MHC I

Complications Due To Low Expression Of MHC I Complexes, As Highlighted By The Examiner, Constitute A Problem That The Claimed Invention Overcomes

The Examiner contends that cancer immunotherapy is limited because "the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen." Yet low expression of MHC I complexes in fact is precisely the problem that the claimed invention overcomes. Instead of trying to induce tumor cells to express a costimulatory molecule of surface of a cell, per a conventional approach, the invention uses soluble costimulatory factor, which is secreted by tumor cells, and does not require MHC class I presentation. Indeed, the Neuro2a cells that applicants used to show the effect of soluble B7-1 gene therapy express very low levels MHC class I. Thus, the present invention dispenses with the need for MHC I complex presentation to induce an immune response; hence, the Examiner's stated concern is inapposite to the present case.

Alleged Non-Enablement Due to Invention Being Related to Gene Therapy

The Examiner's Concerns Over Clinical Efficacy Of Gene Therapy Do Not Withstand A Close Reading Of A Cited Publication; Moreover, Section 112 Does Not Require A Demonstration Of Efficacy Per Se

Turning to the problems of gene therapy approaches in general, the Examiner cites a 1995 NIH panel report by Orkin, which states that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at any time in humans." This statement is not evidence of non-enablement of the invention, for at least the following reasons.

First, while the Orkin raises concerns about the various application of gene therapy as a whole, Orkin speaks in strongly positive terms, at pages 33 and 34, about gene therapy for treating tumors:

> Dr. Blaese said there is some evidence of efficacy, such as tumor shrinkage in patients with glioblastomas. Some of the protocols call for the gene transfer to procedure to induce immune system responses against the tumor, according to Dr. Gary Nabel. In some cases, patients appear to go into long-term remission; in other cases the effects are transient. Partial effects are commonplace in cancer treatment, and gene therapy approaches therefore may find acceptance as a useful addition to the therapeutic arsenal.

Considering the context of a "gene transfer procedure to induce immune system responses," Orkin notes "some evidence of efficacy, such as tumor shrinkage in patients with glioblastomas," and states that gene therapy "may find acceptance as a useful addition to the therapeutic arsenal." It is important to consider that the passage quoted by the Examiner addresses generally the whole field of gene therapy, and not tumor treatment *per se*. Rather than undercutting the enabling quality of applicants' teachings, a careful reading of Orkin supports the proposition that the present claims are enabled by the original specification.

In addition, the quoted statement addresses "clinical efficacy," which is a term of art employed in the context of regulatory approval for drugs. Efficacy for drugs is determined by the FDA, while enablement for a patent claim is determined by the PTO. "The Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs in the United States." MPEP § 2107.01 (emphasis added). Therefore, a failure to "definitively" demonstrate the "clinical efficacy" of gene therapy in humans in no way reflects a descriptive shortcoming in the application, let alone one that deprives the present claims of "enablement," within the meaning of section 112.

"[I]n regards to the immunotherapy of cancer," the Examiner cites Orkin again for the proposition that, "'while these strategies show promise in mouse models, none has demonstrated efficiency in humans.'" Applicants urge that this statement, read in context, does not evidence non-enablement. The context of this statement is as follows:

> Because of these formidable problems, other-more indirect-gene therapy approaches to the treatment of cancer are being considered. Included among these are transfer of genes for cytokines or other immunemodulatory products to cancer cells either outside the body (*ex vivo*) or directly into the patient (*in vivo*) in an attempt to stimulate immune recognition of not only the gene-modified cancer cells, but also cancer cells that have not received the gene situated elsewhere in the body. In some of instances, tumor infiltrating lymphocytes or other immune effector cells have also been transduced in an attempt to increase their specificity and/and reactivity against tumor cells. Although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans.

None of the indirect-therapy approaches thus implicated is related closely enough to the use of soluble costimulatory molecules, pursuant to the present invention, to provide a reasonable basis for challenge the enabling quality of applicants' teaching vis-à-vis the present claims. As mentioned above, in the context of a "gene transfer to procedure to induce immune system responses," Orkin notes that in "patients" there has been evidence of "some evidence of efficacy, such as tumor shrinkage." Moreover, as discussed above, applicants are not required to show "efficacy" to the PTO to vindicate the enablement of the present claims.

Alleged Non-Enablement For Tumors Other Than Solid Neuroblastoma Tumors

That The Invention Invokes An Immune Response Against A Highly Non-Immunogenic Tumor Validates A Reasonable Conclusion That The Claimed Invention Is Enabled For Other Tumors

The Examiner asserts that the specification only enables growth reduction of "a solid neuroblastoma." But applicants have shown that, with fewer than 1% of Neuro2a cells expressing a soluble costimulatory molecule, one can render immunogenic a non-immunogenic cell line. Indeed, in this regard the non-immunogenic Neuro2a tumor, is one of the most difficult targets for immunogene therapy. See Specifications, page 8, lines 3-10. See also Katsanis et al., Cancer Gene Ther., 2:39-46, (1995); Katsanis et al., Cancer Gene

Ther., 3:75-82, (1996); and Heuer et al.; Hum. Gene Ther., 7:2059-2068, (1996), respectively appended as Exhibits 5, 6, and 7.

In light of these observations, the knowledgeable reader of the present specification would conclude, that the claimed invention allows for the enhancement or activation of a T-cell response. Conversely, there would be no reason for the skilled person, informed by the specification, to believe that the invention might be effective only against a solid neuroblastoma, as the Examiner urges.

Alleged Non-Enablement For Soluble Costimulatory Factors Other Than B7-1-Ig

The Examiner Has Not Established A Prima Facie Case As To A Purported Failure By The Application To Enable, Beyond B7-1-Ig, The Category Of Soluble Costimulatory Molecules

According to the PTO's own rules, the Examiner must provide reasons to challenge the enablement of a given claim. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." MPEP § 2164.04, quoting from *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The "minimum requirement is for the examiner to give reasons for the uncertainty of the enablement." MPEP § 2164, quoting from *In re Bowen*, 492 F.2d 859,862064, 181 USPQ 48, 51 (CCPA 1974).

Without proffering any evidence, the Examiner simply states that the specification does not allow one to make and use other soluble costimulatory molecules other than the working example. The Examiner opines that the "co-stimulatory molecules listed in the specification all have different ligands and mediate or transduce different signal in T cells such that a nexus cannot be drawn between the applicant's working example using B7-1-Ig and other substantially different co-stimulatory molecules."

This sort of broad-brush, conclusory statement does not meet the threshold requirement for a demonstration, by the PTO, that one of skilled in the relevant art could not make or use a costimulatory molecule, given the specific guidance provided in the specification.

The claimed invention is directed to using costimulatory molecules in a gene-therapy method, not to a method of creating members of the family of soluble costimulatory factors,

which was well-known when applicants' priority application was filed. To evidence this last point, applicants attach the following publications: Kanner et al., J. Immunol., 148:2023-9, No. 7, (1992); Kato et al., J. Exp. Med., 176:1241-9, (1992); Hurtado et al., J. Immunol., 155:3360-7, (1995); and Noelle et al., Proc. Natl. Acad. Sci. USA, 89:6550-6554, (1992), marked respectively as Exhibits 1, 2, 3, and 10. Each of these publications teaches how to make various costimulatory molecules. Viewed in light of knowledge that a skilled person has in the area of soluble costimulatory factors, the specification is sufficient to guide the skilled artisan into making and using other costimulatory factors in the present invention. "[A] specification need not disclose what is well known in the art." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). Therefore, with the guidance provided by the specification, in light of the state of the prior art, a skilled artisan would have been able to make and use costimulatory with a reasonable amount of experimentation that would not be considered undue.

The Examiner further argues that there is a failure to teach the level of soluble costimulatory gene expression that correlates with any effect on tumor growth. Applicants urge that such a level could be ascertained by routine experimentation. Evidencing this, applicants attach hereto Todo et al., Cancer Res., 61:, 153-161, (2001) as Exhibit 4, which demonstrates that by practicing an embodiment of the claimed invention, the level of soluble B7 required to invoke immunogenicity, in a non-immunogenic cell, was determined by the applicants and others to be less than 1% of cells. Applicants thereby have demonstrated that the requisite level of soluble costimulatory gene expression indeed is very small, and determining the exact levels for other costimulatory molecules would be routine experimentation for one skilled in the relevant art. Accordingly, the specification enables one of skill in the art to make and use other costimulatory molecules without undue experimentation and therefore withdrawal of this rejection is requested.

Alleged Non-Enablement For Any Type Of Vector Other Than
A Defective Herpes Simplex Virus

Applicants Have Evidenced Sufficiently That The Specification Is Enabling For Targeted Delivery And Expression Of Various Vectors In Tumor Cells

The Examiner further argues that only a defective HSV vector is enabled for the present invention. Yet she has provided no specific evidence of why, given the guidance of the specification, one skilled in the art would not expect the present invention to work with vectors other than a defective herpes simplex virus.

As of October 5, 1999, the priority date of the specification, much was known about the use of various vectors for gene therapy. The prior art was full of guidance in selecting appropriate categories of gene therapy vectors for treating tumors. For example, see Exhibits 8 and 9. Much was known already about which types of vectors are preferred for targeting certain types of tumor cells. As detailed in Fry et al., Expert Reviews, 1-24, (1999), attached as Exhibit 8, before the priority date of the application, at least 3134 patients had been enrolled in 373 gene therapy protocol worldwide. Id. at 20. Over 62% (234) of these protocols were for cancer. Id. One of ordinary skill could select an appropriate vector for a target tumor and practice the invention with a reasonable amount of experimentation. Therefore, in light of the specification, a skilled artisan could practice the present invention without undue experimentation.

Alleged Non-Enablement Due For Any Type Of Delivery Other Than
Intratumoral Administration

The Examiner Marshalls No Evidence To Substantiate Finding The Present Claims Non-Enabled For An Administration MO Other Than Intratumoral Administration

In response to the Examiner's argument that the specification only enables delivery by intratumoral injection cannot stand because there is no evidence of record that other delivery methods would not work. With the guidance provided by the specification, various delivery methods could be tested by one of skill in the art with routine experimentation. Accordingly, applicants request withdrawal of all enablement rejections.

Rejections Under 35 USC §112, Second Paragraph

Claims 1-22 and 24-31 are rejected under 35 USC § 112, second paragraph, for being indefinite for the term "tumor-related cells." In response to the Examiner's request for clarification, applicants define tumor related cells as cells in and around the tumor such as endothelial cells, mesenchymal cells and immune cells.

Rejections Under 35 USC §102(e)

Claims 1, 7-11, 17-25, and 28-32 are rejected under 35 USC § 102(e) as anticipated by U.S. Patent No. 6,310,045, referred to as Berber et al. Applicants respectfully traverse the rejection. Berber does not use a soluble costimulatory factor and therefore cannot anticipate the claims. Berber uses IL-2, which is a cytokine and not a costimulatory factor that is normally expressed on the membrane of antigen presenting cells and required for T cell stimulation.

Rejections Under 35 USC §102(b)

Claims 1, 7-11, 17-25, and 28-32 are rejected under 35 USC § 102(e) as anticipated by Hollenbaugh et al. (1992) EMBO J., Vol. 11 (12), 4313-4321. Applicants respectfully traverse the rejection. Hollenbaugh used soluble gp39 as a tool to examine the gp39-CD40 interaction *in vitro*. There is no teaching of using this method for tumor therapy or gene therapy.

Rejections Under 35 USC §102(a)

Claims 23 and 39 are rejected under 35 USC § 102(a) as anticipated by Sturmhoefel et al. (10/1/99) Canc. Res., Vol. 59(19), 4964-4971. Applicants note, however, that Sturmhoefel used soluble B7-1-Ig or B7-2-Ig protein for systemic administration. The plasmid encoding these factors was used for generating fusion proteins in vitro. This is very different from the present invention in claims 23 or 32, both of which relate to a vector or gene for use in gene therapy.

In light of the foregoing, applicants request the reconsideration and withdrawal of all anticipation rejections.

Objections to Claims 15 and 27

Claims 15 and 27 were objected to because parts of the claims on pages 10 and 11 respectively were hidden by punch holes. Attached are clean copies of pages 10 and 11.

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

April 4, 2002
Date

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

15. The method of claim 1, wherein said factor comprises a dimer.

16. The method of claim 15, wherein the monomers of said dimer are connected by a linker.

17. The method of claim 1, wherein said vector is a viral vector.

18. The method of claim 1, wherein said vector is a non-viral vector.

19. The method of claim 1, wherein said tumor is selected from the group consisting of astrocytoma, oligodendroglioma, meningioma, neurofibroma, glioblastoma, ependymoma, Schwannoma, neurofibrosarcoma, medulloblastoma, germ cell tumor, chordoma, pineal tumor, choroid plexus papilloma, pituitary tumor, and vascular tumor.

20. The method of claim 1, wherein said tumor cells or tumor-related cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, head and neck cancer cells, breast cancer cells, lung cancer cells, colon cancer cells, ovarian cancer cells, renal cancer cells, neuroblastomas, squamous cell carcinomas, hepatoma cells, and mesothelioma and epidermoid carcinoma cells.

21. The method of claim 1, wherein said administering further comprises delivering to said patient at least one expressible nucleotide sequence coding for an immune modulator.

22. The method of claim 21, wherein said immune modulator is selected from the group consisting of a cytokine, a chemokine, and a membrane-bound costimulatory molecule.

23. A pharmaceutical composition comprising (A) a vector that contains gene encoding a soluble costimulatory factor and (B) a pharmaceutically compatible carrier.

24. A gene-therapy method of activating or enhancing a T-cell response in a patient with a tumor, comprising administering to said patient a pharmaceutical composition comprising: an expressible nucleotide sequence for a soluble costimulatory factor such that (i) said factor is expressed by the tumor cells or the tumor-related cells, and (ii) said T-cell response thereby is activated or enhanced against said tumor.

25. The method according to claim 24, wherein said administrating comprises introducing said composition directly into said tumor or a local area of said tumor.

26. The method according to claim 24, wherein said factor is selected from the group consisting of B7-1, B7-2, B7-3, CD40, CD40 ligand, CD72, CD24, LFA-3, ICAM-1, CD70, CD2, CD48, 4-1BB, 4-1BB ligand, and LIGHT.

27. The method according to claim 26, wherein said factor comprises two extracellular domains.

28. The method of claim 24, wherein said tumor is selected from the group consisting of astrocytoma, oligodendroglioma, meningioma, neurofibroma, glioblastoma, ependymoma, Schwannoma, neurofibrosarcoma, medulloblastoma, germ cell tumor, chordoma, pineal tumor, choroid plexus papilloma, pituitary tumor, and vascular tumor.

29. The method of claim 24, wherein said tumor cells or tumor-related cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, head and neck cancer cells, breast cancer cells, lung cancer cells, colon cancer cells, ovarian cancer cells, renal cancer cells, neuroblastomas, squamous cell carcinomas, hepatoma cells and mesothelioma and epidermoid carcinoma cells.

30. The method of claim 24, wherein said administering comprises delivering to said patient at least one expressible nucleotide sequence coding for at least one immune modulator.

31. The method of claim 30, wherein said immune modulator is selected from the group consisting of cytokines, chemokines, and membrane-bound costimulatory molecules.

32. A pharmaceutical composition comprising (A) a gene encoding a soluble costimulatory factor and (B) a pharmaceutically compatible carrier.